

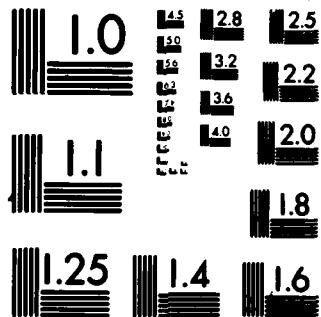
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ARMY ENVIRONMENTAL HYGIENE AGENCY ABERDEEN PROVING GR--ETC F/G 6/20
TOPICAL HAZARD EVALUATION PROGRAM OF CANDIDATE INSECT REPELLENT--ETC(U)
DEC 80 M J TOPPER, M H WEEKS

UNCLASSIFIED USAEHA-75-51-0159-R1

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UNITED STATES ARMY ENVIRONMENTAL HYGIENE AGENCY

ABERDEEN PROVING GROUND, MD 21010

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(16) Michael J. Topper
Maurice H. Weeks

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REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
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4. TITLE (If Applicable) Topical Hazard Evaluation Program of Candidate Insect Repellents AI3-37329-a and AI3-37331-a, USDA Proprietary Chemicals, Study Nos. 75-51-0159-81, Oct 78-Dec 80		5. TYPE OF REPORT & PERIOD COVERED Final - Oct 78 - Dec 80
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11. CONTROLLING OFFICE NAME AND ADDRESS Commander US Army Health Services Command Fort Sam Houston, TX 78234		12. REPORT DATE Oct 78 - Dec 80
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19. KEY WORDS (Continue on reverse side if necessary and identify by block number) USDA Proprietary Chemicals AI3-37329-a AI3-37331-a Topical Hazard Evaluation Candidate repellent Skin irritation Eye irritation Photochemical irritation ALD Guinea pig sensitization test		
20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Preliminary hazard evaluations of AI3-37329-a and AI3-37331-a were performed by means of laboratory animal studies using rats, rabbits and guinea pigs. The technical grade chemicals were noninjurious to the eye, and did not demonstrate potential for causing skin or photochemical irritation or sensitize guinea pigs or demonstrate an acute ingestion hazard. It was recommended that AI3-37329-a and AI3-37331-a, be approved for further testing as a candidate test repellent.		



DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010

CPT Topper/jg/AUTOVON
584-3980

REPLY TO
ATTENTION OF
HSE-LT-T/WP

9 MAR 1981

SUBJECT: Topical Hazard Evaluation Program of Candidate Insect Repellents
AI3-37329-a and AI3-37331-a, US Department of Agriculture
Proprietary Chemicals, Study Numbers 75-51-0159-81 and
75-51-0161-81, October 1978 - December 1980

Executive Secretary
Armed Forces Pest Management Board
Forest Glen Section, WRAMC
Washington, DC 20012

A summary of the pertinent findings and recommendations of the inclosed report follows:

Preliminary hazard evaluations of AI3-37329-a and AI3-37331-a were performed by means of laboratory animal studies using rats, rabbits, and guinea pigs. The technical grade chemicals did not cause skin, eye, or photo irritation. They did not prove to be skin sensitizers or to be acutely toxic by ingestion. It was recommended that both chemicals be approved for further testing as candidate insect repellents.

FOR THE COMMANDER:

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as (5 cy)

Salvad H (age)
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USDA, ARS (Dr. Terrence McGovern)
USDA, ARS-Southern Region

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DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010

REPLY TO
ATTENTION OF

HSE-LT-T/WP

TOPICAL HAZARD EVALUATION PROGRAM
OF CANDIDATE INSECT REPELLENTS
AI3-37329-a and AI3-37331-a
US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICALS
STUDY NUMBERS 75-51-0159-81 and 75-51-0161-81
OCTOBER 1978 - DECEMBER 1980

1. AUTHORITY.

a. Letter, US Department of Agriculture - Agricultural Research Service, Southern Region, Insects Affecting Man Research Laboratory, Gainesville, Florida, 13 October 1978.

b. Memorandum of Understanding between the US Army Environmental Hygiene Agency; the US Army Health Services Command; the Department of the Army, Office of The Surgeon General; the Armed Forces Pest Control Board; and the US Department of Agriculture, Agricultural Research, Science and Education Administration, titled, Coordination of Biological and Toxicological Testing of Pesticides, effective 23 January 1979.

2. REFERENCE. Toxicology Division Procedural Guide, US Army Environmental Hygiene Agency (USAEEHA), 1972, revised 1976.

3. PURPOSE. The purpose of this program is to provide guidance for further entomological testing of the candidate insect repellents AI3-37329-a and AI3-37331-a.

4. SUMMARY OF FINDINGS. Hazard evaluations of the candidate repellents AI3-37329-a and AI3-37331-a were conducted by this Agency using New Zealand White rabbits for skin and eye studies, Hartley guinea pigs for a skin sensitization study and Sprague-Dawley rats for determination of oral toxicity. A tabular presentation of animal toxicity data developed in this Agency follow:^{*†}

* In conducting the studies described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," US Department of Health, Education and Welfare Publication No. (NIH) 74-23, revised 1978.

† The experiments reported herein were performed in animal facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care.

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Study Nos. 75-51-0159-81 and 75-51-0161-81, Oct 1978 - Dec 1980

TABLE. PRESENTATION OF DATA

Test	Results	Interpretation
<u>SKIN IRRITATION STUDIES</u>		
Rabbits		
Single 24-hour application to intact and abraded skin of New Zealand White rabbits.	Chemicals AI3-37329-a and AI3-37331-a did not cause any irritation of the intact skin or of the skin surrounding an abrasion.	USAEHA Category I (ref Appendix A)
0.5 mL technical grade chemical applied to each of six rabbits.	(See Appendices B and C for details.)	
<u>EYE IRRITATION STUDIES</u>		
Rabbits		
Single 24-hour application of 0.1 mL technical grade chemical to one eye of each of six New Zealand White rabbits.	Chemicals AI3-37329-a and AI3-37331-a did not cause any irritation to the eyes of rabbits. (See Appendices D and E for details.)	USAEHA Category A (ref Appendix A)
<u>APPROXIMATE LETHAL DOSE (ALD)</u>		
Oral		
Rats (male)-no diluent	Chemical AI3-37329-a ALD > 9700 mg/kg Chemical AI3-37331-a ALD = 4300 mg/kg	Neither chemical presents a Tethal hazard from accidental ingestion.

Study Nos. 75-51-0159-81 and 75-51-0161-81, Oct 1978 - Dec 1980

Test	Results	Interpretation
<u>PHOTOCHEMICAL SKIN IRRITATION STUDIES</u>		
<u>Rabbits</u>		
A single 0.05 mL application of a 25 percent (w/v) solution of each chemical and a 10 percent (w/v) Oil of Bergamot solution (positive control) in 95 percent ethyl alcohol were applied to the intact skin of six rabbits. Five minutes after application, the rabbits were exposed to UV light (365 nm) for 30 minutes at a distance of 10-15 cm.	Chemicals AI3-37329-a and AI3-37331-a did not cause a photochemical irritation reaction under test conditions. (See Appendices F and G for details.)	Chemicals AI3-37329-a and AI3-37331-a did not cause a photochemical irritation reaction under test conditions and are not expected to cause a photochemical irritation in humans.
<u>Control</u>		
Following UV exposures of the rabbits, 0.05 mL of test chemical, positive control and diluent were applied to additional skin areas to serve as unirradiated control sites. Application areas were checked for skin irritation at 24, 48 and 72 hours.	Positive control application and irradiation cause greater irritant effects than in unirradiated skin areas.	

Study Nos. 75-51-0159-81 and 75-51-0161-81, Oct 1978 - Dec 1980

Test	Results	Interpretation	
<u>SENSITIZATION STUDIES</u>			
<u>Guinea Pigs (Male)</u>			
Intradermal injections of 0.1 mL of a 0.1 percent solution (w/v) of AI3-37329-a and AI3-37331-a.	Ten test guinea pigs for each chemical were given 10 sensitizing doses over a 3-week period. After 2 weeks rest, they were challenged with ID injections of each test compound.	Challenge doses of test chemicals did not produce a sensitization reaction. (See Appendices H and I for details.)	Chemicals AI3-37329-a and AI3-37331-a did not produce sensitization reactions under test conditions and are not expected to produce sensitization reactions in man.

5. CONCLUSION. Technical grade chemicals AI3-37329-a and AI3-37331-a did not cause any skin, eye, or photo irritation, no sensitization reaction, and did not prove to be an acute ingestion hazard.

6. RECOMMENDATION. Under the provisions of the Memorandum of Understanding (paragraph 1b), it is recommended that AI3-37329-a and AI3-37331-a be approved for further testing as candidate insect repellents.



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Chief, Toxicity Evaluation Branch
Toxicology Division

APPROVED:



ARTHUR H. MCCREESH, Ph.D.
Chief, Toxicology Division

APPENDIX A

TOPICAL HAZARD EVALUATION PROGRAM
DEFINITIONS OF CATEGORIES OF COMPOUNDS BEING
CONSIDERED FOR ACUTE SKIN APPLICATION

CATEGORY I - Compounds producing no primary irritation of the intact skin or no greater than mild primary irritation of the skin surrounding an abrasion. (INTERPRETATION: No restriction for acute application to the human skin.)

CATEGORY II - Compounds producing mild primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should be used only on human skin found by examination to have no abrasions or may be used as a clothing impregnant.)

CATEGORY III - Compounds producing moderate primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should not be used directly on the skin without a prophetic patch test having been conducted on humans to determine irritation potential to human skin. May be used without patch testing, with extreme caution, as clothing impregnants. Compound should be resubmitted in the form and at the intended use concentration so that its irritation potential can be reexamined using other test techniques on animals.)

CATEGORY IV - Compounds producing moderate to severe primary irritation of the intact skin and of the skin surrounding an abrasion and, in addition, producing necrosis, vesiculation, and/or eschars. (INTERPRETATION: Should be resubmitted for testing in the form and at the intended use concentration. Upon resubmission, its irritation potential will be reexamined using other test techniques on animals, prior to possible prophetic patch testing in humans, at concentrations which have been shown not to produce primary irritation in animals.)

CATEGORY V - Compounds impossible to classify because of staining of the skin or other masking effects owing to physical properties of the compound. (INTERPRETATION: Not suitable for use on humans.)

EYE CATEGORIES:

A. Compounds noninjurious to the eye. INTERPRETATION: Irritation of human eyes is not expected if the compound should accidentally get into the eyes, provided it is washed out as soon as possible.

B. Compounds producing mild injury to the cornea. INTERPRETATION: Should be used with caution around the eyes.

C. Compounds producing mild injury to the cornea, and in addition some injury to the conjunctiva. INTERPRETATION: Should be used with caution around the eyes and mucosa.

D. Compounds producing moderate injury to the cornea. INTERPRETATION: Should be used with extreme caution around the eyes.

E. Compounds producing moderate injury to the cornea, and in addition producing some injury to the conjunctiva. INTERPRETATION: Should be used with extreme caution around the eyes and mucosa.

F. Compounds producing severe injury to the cornea and to the conjunctiva. INTERPRETATION: Should be used with extreme caution. It is recommended that use be restricted to areas other than the face.

Study Nos. 75-51-0159-81 and 75-51-0161-81, Oct 1978 - Dec 1980

APPENDIX B

COMPOUND: A13-37329-a, USDA PROPRIETARY CHEMICAL		USAEHA STUDY NO. 75-51-0159-81		CONDITIONS - 0.5 mL of chemical was applied to 3 abraded and 3 intact skin sites. The sites were covered for 24 hrs with gauze	
PRIMARY SKIN EFFECTS NEW ZEALAND WHITE RABBITS	USAEHA TOXICITY CATEGORY I	Time of Observation Hours	Comments		
			Response Rabbit No.	Score	
Erythema & Eschar		900 901 902 903 904 905			
Intact Skin	24	1	0	0	0
Intact Skin	72	0	0	0	0
Abraded Skin	24	0	0	0	0
Abraded Skin	72	0	0	0	0
			Subtotal	1	
Edema Formation					
Intact Skin	24	0	0	0	0
Intact Skin	72	0	0	0	0
Abraded Skin	24	0	0	0	0
Abraded Skin	72	0	0	0	0
			Subtotal	0	
			Total	1	
			Mean	0.08	

Study Nos. 75-51-0159-81 and 75-51-0161-81, Oct 1978 - Dec 1980

APPENDIX C

COMPOUND: A13-37331-a, USDA PROPRIETARY CHEMICAL PRIMARY SKIN EFFECTS NEW ZEALAND WHITE RABBITS		USAETA TOXICITY CATEGORY 1		USAEHA STUDY NO. 75-51-0161-81					
	Time of Observation Hours	Response Rabbit No.		SCORE	Comments				
		900	901	902	903	904	905		
<u>Erythema & Eschar</u>									
Intact Skin	24	0	0	0	0	0	0	0	0
Intact Skin	72	0	0	0	0	0	0	0	0
Abraded Skin	24	0	0	0	0	0	0	0	0
Abraded Skin	72	0	0	0	0	0	0	0	0
<u>Edema Formation</u>									
Intact Skin	24	0	0	0	0	0	0	0	0
Intact Skin	72	0	0	0	0	0	0	0	0
Abraded Skin	24	0	0	0	0	0	0	0	0
Abraded Skin	72	0	0	0	0	0	0	0	0

APPENDIX D

COMPOUND: A13-37329-a, USDA PROPRIETARY CHEMICAL

ACUTE EYE EFFECTS
NEW ZEALAND WHITE RABBITSUSAEHA TOXICITY CATEGORY
ACONDITIONS - 0.1 mL of the chemical was put into
the right eye of six rabbits. The left eye served as a
control.

Time of Reading Hrs-Days	Structure	STUDY NO. 75-51-0159-81							
		749	750	751	Rabbit No. 752	753	754	Mean Score	Comments
24	cornea iris conjunctivae	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0	
48	cornea iris conjunctivae	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0	
72	cornea iris conjunctivae	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0	
7-days	cornea iris conjunctivae	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0	

APPENDIX E

COMPOUND: AI3-37331-a., USDA PROPRIETARY CHEMICAL

ACUTE EYE EFFECTS
NEW ZEALAND WHITE RABBITSUSAEHA TOXICITY CATEGORY
A

CONDITIONS - 0.1 mL of chemical was applied into right eye of six rabbits. The left eye served as a control.

STUDY NO. 75-51-0161-81

Time of Reading Hrs-Days	Structure		Scores				Mean Score	Comments
			761	762	763	764		
24	cornea iris conjunctivae		0 0 2	0 0 4	0 0 0	0 0 4	0 0 2	0 0 2.66
48	cornea iris conjunctivae		0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0
72	cornea iris conjunctivae		0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0
7-days	cornea iris conjunctivae		0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0

APPENDIX F

Compound: A13-37329-a, USDA PROPRIETARY CHEMICAL USAEHA STUDY NO. 75-51-0159-81

Photochemical Irritation

Comments:

New Zealand White Rabbits Procedure: A 25% (w/v) solution of the chemical in 95% ethanol was applied to the skin of six rabbits. One side of the back of the rabbit was exposed to UV light for 30 minutes.

Observation Time	Test Chemical		Test Chemical		Positive Control		Positive Control	
	UV Exposure		Non-UV Exposure		UV Exposure		Non-UV Exposure	
	Erythema	Edema	Erythema	Edema	Erythema	Edema	Erythema	Edema
24 Hours	11	4	11	4	18	16	10	1
48 Hours	12	5	10	4	15	14	8	3
72 Hours	10	5	10	3	12	11	4	2
Total Irritant Responses	33	14	31	11	45	41	22	6
Mean	1.83	0.78	1.72	0.61	2.50	2.28	1.22	0.33

APPENDIX G

Compound: A13-37331-a, USDA PROPRIETARY CHEMICAL

USAEHA STUDY NO. 75-51-0161-79

<u>Photochemical Irritation</u>	<u>Comments:</u>
New Zealand White Rabbits	Procedure: A 25% (w/v) solution of the chemical in 95% ethanol was applied to the skin of six rabbits. One side of the back of the rabbits was exposed to UV light for 30 minutes.

<u>Observation Time</u>	MEAN SKIN IRRITATION SCORE					
	Test Chemical		Positive Control		Positive Control	
	UV Exposure	Non-UV Exposure	UV Exposure	Non-UV Exposure	Erythema	Edema
24 Hours	12	4	12	1	18	—
48 Hours	5	1	2	0	15	14
72 Hours	2	1	1	0	12	11
Total Irritant Responses	19	6	15	1	45	41
Mean	1.06	0.33	0.83	0.06	2.50	2.28
					1	0.33

APPENDIX H

COMPOUND: AI3-37329-a, USDA PROPRIETARY CHEMICAL		USAEHA STUDY NO. 75-51-0159-81	
GUINEA PIG SENSITIZATION MALE HARTLEY STRAIN		<u>Substance:</u> AI3-37329-a	
		<u>Identity:</u>	
		<u>Positive Control:</u>	
24 Hrs	Mean Body Weight (g)	Diluent	Test Compound
	Initial	Initial	Initial
Test Cmpd	576	800	2.6
Positive Control			2.7
			47
			45
48 Hrs	Mean Body Weight (g)	Diluent	Test Compound
	Initial	Final	Initial
Test Cmpd	---	---	---
Positive Control		0	0
			29
			30

APPENDIX I

COMPOUND: AI3-37331-a, USDA PROPRIETARY CHEMICAL		USAECIA STUDY NO. 75-51-0159-81	
GUINEA PIG SENSITIZATION MALE BARTLEY STRAIN		Substance: AI3-37331-a	
		<u>Identity:</u> <u>Positive Control:</u>	
24 Hrs	Mean Body Weight (g)	Diluent	Test Compound
	Initial Final	Initial Final	Initial Final
rest Cmpd	626	844	1.8
Positive Control		0	30
			45
48 Hrs	Mean Body Weight (g)	Diluent	Test Compound
	Initial Final	Initial Final	Initial Final
rest Cmpd	---	---	0
Positive Control		0	14.9
			14.7

